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# TITLE

PROCESS FOR MAKING GRANULATED N-[N-(3,3-DIMETHYLBUTYL)-  
 L- $\alpha$ -ASPARTYL]-L-PHENYLALANINE 1-METHYL ESTER

This application claims the benefit of U.S. Provisional  
 Patent Application No. 60/182,908, filed February 16,  
 2000.

## BACKGROUND OF THE INVENTION

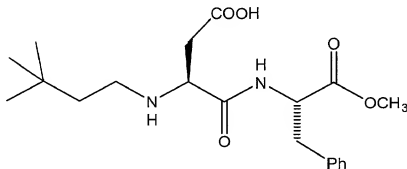
### Field of the Invention

- 5 This invention relates to the formation of granules of  
 N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine  
 1-methyl ester (neotame) by compaction and size  
 reduction. Neotame is converted from a light powder to  
 relatively dustless, free-flowing granules suitable for
- 10 use in a variety of applications. This invention also  
 relates to food products sweetened with the neotame  
 granules, as well as to methods of preparing such food  
 products.

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# Related Background Art

It is known that N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -  
aspartyl]-phenylalanine 1-methyl ester (neotame) is an  
5 extremely potent sweetening agent (about 8000X sweeter  
than sugar) that has the formula



10 Clearly, the use of a high potency sweetener such as  
N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine  
1-methyl ester requires consideration of the ability to  
deliver the sweetener in a given application. Thus,  
effective means for delivering neotame in desired  
15 compositions are very useful.

Pressure agglomeration techniques are employed in a  
variety of industries, including the pharmaceutical,  
agricultural and mining industries. These techniques  
20 are employed primarily as size enlargement processes.  
Wolfgang Pietsch, Size Enlargement by Agglomeration,  
John Wiley & Sons, pp. 218-221 (1991). Examples of  
such pressure agglomeration techniques include roller  
compaction, tableting, slugging, ram extrusion, plunger  
25 pressing, roller briquetting, reciprocating piston  
processing, die pressing and pelleting.

5 "Roller Compaction Technology", Handbook of  
Pharmaceutical Granulation Techniques, Marcel Dekker,  
Inc., pp. 99-150 (1997). Typically, roller compaction  
is used in conjunction with an appropriate size  
reduction process. Further, roller compaction and  
10 optional size reduction is known in the food  
ingredient, chemical and plastic industries as well.

25

The granulation of  $\alpha$ -L-aspartyl-L-phenylalanine or aspartame is known in the sweetener industry. U.S. Patent No. 5,473,097 describes aspartame having improved solubility characteristics, obtained by granulating the aspartame to a grain size of 100-1400 $\mu$ m. The '097 patent discloses that such granulation can be accomplished by any known method of

mixing granulation, including powder compression granulation.

U.S. Patent No. 5,358,186 describes a process for the  
5 reduction or prevention of the formation of fine,  
powdery dipeptide sweeteners, in particular, aspartame.  
According to the method of the '186 patent, aspartame  
is compacted, broken down, passed through a special  
screen or perforated plate having pore diameters from  
10 1-10mm, then further broken down and classified into  
various particle sizes.

It is important to note that certain particle sizes of  
a given material may be more useful for certain  
15 applications. For example, U.S. Patent No. 5,834,018  
discloses that aspartame particles having a very narrow  
particle size distribution, in which 97 wt.% of the  
particles are larger than 20-40  $\mu\text{m}$  and 97 wt.% of the  
particles are smaller than 250-205  $\mu\text{m}$ , are particularly  
20 suitable for use in tablets, powders and chewing gums.  
This is due to the granules' high dissolution rate,  
good flow properties, good dispersibility, little dust  
formation and virtual absence of electrostatic  
charging.

25  
Granules of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-  
phenylalanine 1-methyl ester formed by compaction and  
size reduction are not disclosed or suggested by the  
aforementioned art.

30

# SUMMARY OF THE INVENTION

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The present invention is directed to a process for forming granules of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine 1-methyl ester. This process comprises the steps of (a) compacting N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine 1-methyl ester powder to form compacts; (b) breaking up said compacts to form granules; and, optionally, (c) screening said granules to obtain granules of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine 1-methyl ester having a desired particle size.

In a preferred embodiment of the present invention, the compacting step is accomplished using roller compaction; the compacts take the form of flakes or chips. In further preferred embodiments of the present invention, the breaking up step is accomplished using a mill.

This invention is further directed to granules of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine 1-methyl ester made according to the process of the present invention.

Additional embodiments of the present invention are directed to food products sweetened with such granules of neotame and to methods of sweetening food products with the granules of neotame of this invention.

30

#### DETAILED DESCRIPTION

Generally, N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine 1-methyl ester (neotame) exists as a light, somewhat dusty powder. It is important to note that neotame powder is not very easy to use or handle due to its dusting tendencies and poor flowability properties. The extreme potency of neotame exacerbates the problems associated with dusting, e.g., loss of material, dust contamination of other products, and human irritability with respect to the highly potent neotame dust. Neotame's extreme potency also presents unique problems with respect to delivery including the manipulation of very small amounts of neotame and the preservation of homogeneity. Thus, it is desirable to granulate neotame to reduce dusting and thereby minimize loss, to improve flowability and to provide an acceptable delivery form.

Neotame granulation may be accomplished using any known wet or dry granulation processes like spray granulation using a wet binder with or without fluidization, powder compaction, pulverizing, extrusion, tumble agglomeration, etc. However, dry granulation such as powder compaction is most attractive due to its simplicity.

Compaction, preferably roller compaction, with size reduction can be used as a particle formation technique to form relatively dustless, free flowing granules of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine 1-methyl ester. As used herein, the term "granules"

refers to free-flowing, relatively non-dusty,  
mechanically strong particles of N-[N-(3,3-  
dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine 1-methyl  
ester.

5

The granules of the present invention have better  
handling properties and flowability than neotame  
powder. Typically, the granules of the present  
invention have a higher bulk density than neotame  
10 powder. Compaction of neotame also helps to eliminate  
the loss of this valuable and potent material through  
dust. The granulation process of the present invention  
comprises compaction, preferably roller compaction,  
followed by size reduction and optional size  
15 classification to obtain the desired particle size  
range.

In particular, neotame is first compacted into compacts  
and then milled and classified to remove "overs" and  
20 "fines" to obtain neotame granules of the desired  
particle size range. As used herein, the term "overs"  
refers to material larger than the largest particle  
size desired, and the term "fines" refers to material  
smaller than the smallest particle size desired. Overs  
25 are typically milled again to obtain desired particle  
sizes, and fines are typically recycled and  
recompact.

Hence, one embodiment of the present invention is  
30 directed to a process by which granules of neotame are  
formed using compaction.

In the first step of this process, neotame powder is compacted into compacts.

Compaction can be accomplished using any known  
5 compaction technique. Suitable techniques include, without limitation, roller compaction, tableting, slugging, ram extrusion, plunger pressing, roller briquetting, reciprocating piston processing, die pressing and pelleting. Because neotame has a low  
10 melting point ( $-82^{\circ}\text{C}$ ) as compared to other artificial sweeteners, it may be desirable to reduce the possibility of heat generation by employing a cooling means during compaction. For example, roller compactors are currently available which are equipped  
15 with means for cooling the rollers.

The compacts may take any form that can be subjected to subsequent size reduction. Suitable forms include, without limitation, flakes, chips, briquets, chunks,  
20 and pellets. The shape and appearance of the compacts vary depending upon the shape and surface characteristics of the equipment used to perform the compacting step. Accordingly, the compacts may appear smooth, corrugated, fluted or pillow-pocketed. The  
25 actual size and characteristics of the compacts depend upon the type of equipment and operation parameters employed during compaction.

Any powdered form of neotame may be used in the  
30 compositions of this invention. U.S. Patent No. 5,480,668, U.S. Patent No. 5,510,508 and U.S. Patent No. 5,728,862, which describe the preparation of



neotame are incorporated by reference herein. Further, salts and metal complexes of neotame may be used, such as disclosed in U.S. Patent Application No. 09/146,963, U.S. Patent Application No. 09/146,964, U.S. Patent Application No. 09/148,134, and U.S. Patent Application No. 09/146,965, all filed September 4, 1998, and all of which are incorporated by reference herein. The anhydrous form of neotame is suitable for use in this invention, as well as the various crystalline forms of neotame. Other exemplary forms of neotame that may be useful in this invention include cyclodextrin/neotame complexes such as disclosed in U.S. Provisional Patent Application No. 60/100,867 and co-crystallized neotame disclosed in U.S. Patent Application No. 09/154,568, both filed September 17, 1998, the disclosure of both of which are incorporated by reference herein.

Neotame may be present in a compact or granule of the present invention in any amount from 0.01% to 100% by weight. Clearly, the amount of neotame depends on a variety of factors including the presence and identity of other compact or granule components and the desired end use for the resultant granule.

It is possible, and, in fact, it is desirable to deaerate the neotame powder prior to compaction. Such deaeration leads to more effective compaction and the formation of stronger compacts and resultant granules. Deaeration may be accomplished through any known means, including, without limitation, screw feeding, vacuum deaeration and combinations thereof.

Optionally, a dry binder may be mixed with the neotame powder prior to compaction. Ultimately, the use of a dry binder improves the strength of the granules and also aids in their dispersion in liquids. P.J.

- 5 Sheskey, "Evaluation of Various Polymers as Dry Binders in the Preparation of an Immediate-Release Tablet Formulation by Roller Compaction", Pharm. Tech., vol. 19, pp. 98-112 (1995). Suitable dry binders include, without limitation, pregelatinized corn starch,  
10 microcrystalline cellulose, hydrophilic polymers (such as methyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, alginates, xanthan gum, gellan gum, and gum arabic) and mixtures thereof. Preferably, the binder is  
15 hydroxypropylmethyl cellulose.

The dry binder is generally used in amount from about 0.1% to about 40% by weight of the neotame powder.

- Preferably, the dry binder is used in an amount from  
20 about 1% to about 20% by weight of the neotame powder.

In a preferred embodiment of this invention, neotame powder is compacted into flakes or chips using a roller compactor.

25

Typically, as described in "Roller Compaction Technology" by Ronald W. Miller, Handbook of Pharmaceutical Granulation Technology, Marcel Dekker, Inc., pp. 99-150 (1997), compaction of a powder (with  
30 or without dry binder) is accomplished using a conventional roller compaction apparatus. Such an apparatus usually consists of a hopper for feeding the

powder to be compacted and a pair of counter-rotating rolls. The powder may be fed to the apparatus through the hopper by gravity or by a force-feed screw. Either or both rolls are fixed onto their axes, with one roll  
5 optionally slightly moveable.

According to the present invention, neotame is fed into the hopper and is drawn into the nip angle area. The neotame is then drawn near the roll pair and is  
10 predensified. Then the neotame is drawn into the roll gap, and there it is compacted and plastic deformation occurs. Long, thick flakes or chips of neotame are obtained as a result of this processing. The actual size of the compacts depends upon the width of the roll  
15 and the scale of the equipment employed. The characteristics of the compacts, such as hardness, density and thickness, depend on factors including pressure, roll speed, feed rate and feed screw amps employed during the compaction process.

20 In the second step of the process of the present invention, the neotame compacts are broken up to form granules. This can be accomplished by any known means, including a mill. The breaking up step may be  
25 accomplished in a single step or it may preferably be accomplished through a series of steps, using a variety of opening sizes for the mill. In this way, the amount of fines produced may be reduced. Typically, granulation or breaking up is accomplished in two  
30 steps, namely, a course breaking step and a subsequent milling step.

As a result of this second step, neotame granules of varying size are obtained. A final and optional step in the process of the present invention is screening the granules to obtain granules of a desired particle size range. This step can be accomplished by any conventional means for screening particles, including screeners and sifters.

Another optional step in the method of the present invention is a recycling step. According to the recycling step of the present method, the neotame fines resulting from the size reduction step are recycled back to the compactor feed.

The neotame granules of this invention typically have a particle size ranging from about 20 to about 200 mesh. Preferably, the granules have a particle size ranging from about 20 to about 60 mesh, from about 60 to about 100 mesh, from about 100 to about 200 mesh, or through 200 mesh. The particle size range varies depending on the device used in the second step of the present process.

Importantly, certain size granules of the present invention may be particularly suitable for use in certain applications, given the improved properties of the inventive granules over the neotame powder (i.e., bulk density, flowability and dissolution). For example, granules ranging from 20 to 60 mesh or 60 to 100 mesh may be particularly suitable for use in fruit preparations and liquid beverages (i.e., liquid applications). Additionally, particles ranging from

100 to 200 mesh may be particularly suitable for use in powdered soft drinks, dry dessert mixes, ice creams and yogurts. Further, granules having a particle size through 200 mesh may be particularly suitable for use  
5 in dry mixes, refrigerated and frozen products and chewable tablets and may be particularly suited for encapsulation for use in confections and baked goods.

The granules of neotame of the present invention are  
10 suitable for use in any food composition to supplement or replace natural sweeteners, as well as other high intensity sweeteners, normally used as sweeteners. The term food as used herein includes, for example, beverages, fluid dairy products, condiments, baked  
15 goods, frostings, bakery fillings, cereals, nutraceuticals, gelatins, candy and chewing gum. In that regard, the disclosures of copending U.S. Patent Application Nos. 09/213,263, 09/213,860 and 09/215,460, all filed December 17, 1998, directed to the use of  
20 neotame in dairy products, baked goods and beverages, respectively, are incorporated by reference herein. Further, the disclosures of copending U.S. Patent Application No. 09/465,402, filed December 17, 1999, and copending U.S. Provisional Patent Application Nos.  
25 60/125,617, filed March 22, 1999, 60/126,191, filed March 25, 1999, and 60/126,654, filed March 29, 1999, directed to the use of neotame in chewing gum, cereals, gelatins and nutraceuticals, respectively, are incorporated by reference herein. The neotame granules  
30 of the present invention are also suitable for use in any table-top composition. In that regard, the disclosure of copending U.S. Patent Application No.

09/215,461, filed December 17, 1998, directed to the use of neotame in table-top compositions is incorporated by reference herein.

- 5 This invention is also directed to food or table-top compositions, such as described above, containing an effective amount of the neotame granules of the present invention to sweeten the food or table-top composition. Determination of the amount of neotame granules to be  
10 added to the food or table-top composition can be readily determined by one of ordinary skill in the art.

- The granules of neotame of the present invention can be used for these purposes alone or in combination with  
15 known bulking agents. Such bulking agents can be mixed with neotame powder prior to compaction or mixed with the final neotame granules of the present invention. Such a bulking agent is generally used in an amount from about 25% to about 99.99% by weight of the neotame  
20 powder, and preferably from about 50% to about 99.99% by weight of the neotame powder. Suitable bulking agents include, but are not limited to, dextrose, maltodextrin, lactose, inulin, polyols, polydextrose, cellulose and cellulose derivatives and organic acids  
25 including, but not limited to, citric acid and malic acid. Such a product may be suitable for use especially for table-top sweeteners, tablet granulations and powdered soft drinks.

- 30 The neotame granules of this invention may be used in combination with known natural sweeteners as well as other high intensity sweeteners. Such sweeteners can

be mixed with neotame powder prior to compaction or mixed with the final neotame granules of the present invention. Such a sweetener is generally used in an amount from about 0.01% to about 99.99% by weight of the neotame powder, and preferably from about 1% to about 99% by weight of the neotame powder. Sweeteners that may be employed include, without limitation, aspartame, acesulfame salts (e.g., acesulfame-K), sucralose, saccharin, alitame, cyclamates, stevia derivatives, thaumatin, sucrose (liquid and granulated), high fructose corn syrup, high conversion corn syrup, crystalline fructose, glucose (dextrose), polyol sugar alcohols, invert sugar and mixtures thereof.

The neotame granules of this invention may be used in combination with known taste-modifying additives such as those disclosed in U.S. Provisional Patent Application Nos. 60/134,058 or 60/134,064, both filed May 13, 1999, the disclosures of both of which are incorporated by reference herein. Such taste-modifying additives can be mixed with neotame powder prior to compaction or mixed with the final neotame granules of the present invention.

The neotame granules of the present invention are particularly suitable for use in table-top compositions and powdered soft drink mixes. Hence, certain embodiments of the present invention are directed to methods for preparing these. Table-top sweeteners and powdered soft drink mixes can be made according to the present invention by forming a premix of a sweetening

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effective amount of neotame, a binding agent and a carrier, compacting the premix to form compacts; and breaking up the compacts to form granules. In these embodiments, the binding agent includes, without  
5 limitation, maltodextrin, dextrose-maltodextrin blends, hydroxypropylmethyl cellulose, carboxymethyl cellulose, polyvinylpyrrolidone, sucrose and mixtures thereof. Likewise, the carrier includes, without limitation, dextrose, citric acid, maltodextrin, dextrose-  
10 maltodextrin blends, lactose, inulin, erythritol, sorbitol, sucrose, aspartame, acesulfame salts, sucralose, cyclamate, saccharin, stevioside, alitame and mixtures thereof. Both the binding agent and the carrier may be the same.

15 A table-top sweetener comprising the present granules of neotame may also include any other ingredients commonly present in table-top sweeteners in order to tailor the taste of the product to a specific end use.  
20 A table-top sweetener comprising the present granules of neotame may take any known form. Suitable forms include, but are not limited to, sachets including the sweetener in powder or granular form, tablets, liquid sweeteners, and jar, pouches, pocket or other forms in  
25 which the sweetener may be measured in, for example, spoon for spoon form.

An additional embodiment of the present invention is directed to a process for preparing a blend of neotame  
30 granules and a blending agent by forming neotame granules as described in detail above and then dry blending the granules with a blending agent. In this



embodiment, the blending agent includes, without limitation, aspartame, acesulfame salts, sucralose, saccharin, alitame, cyclamates, stevia derivatives, thaumatin, sucrose, fructose, dextrose, polyol sugar  
5 alcohols, dextrose, citric acid, dextrin, maltodextrin, dextrose-maltodextrin blends, lactose, inulin, erythritol, sorbitol, stevioside, hydroxypropylmethyl cellulose, carboxymethyl cellulose, polyvinylpyrrolidone, N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -  
10 aspartyl]-L-phenylalanine 1-methyl ester and mixtures thereof.

The Examples which follow are intended as an illustration of certain preferred embodiments of the  
15 invention, and no limitation of the invention is implied.

#### EXAMPLE 1

20 Four samples of neotame were granulated using the following roller compaction method. Roller compaction was effected for each of the samples using a lab scale TF-Mini roller compactor (Vector Corp., Marion, IA) according to the parameters given in Table 1.

Table 1. Roller Compaction Parameters.

sample	roll speed (rpm)	feed speed (rpm)	roll pressure (kg/cm <sup>2</sup> )
1	5	25	80
2	6	25	80
3	6	25	80
4	5	25	80

Long flakes (6-7") were obtained which discharged in between the rolls vertically without sticking to the roll surfaces. The roller compaction process lasted about 5 minutes for each sample. Long flakes of neotame were obtained. The flakes were analyzed for thickness, density (loose and packed), moisture, melting point and hardness. The results are shown in Table 2.

Hardness was determined using a ball and pan hardness test as described below. Approximately 75 g of the neotame to be tested was screened on an 80 mesh screen and shaken with a Ro-Tap testing sieve shaker (model B, CE Tyler Combustion Engineering, Inc., Mentor, OH) for ten minutes with a hammer. About 50 g +/- 1 g of the neotame retained on the 80 mesh screen was transferred to the pan of the screen assembly. Ten 0.5" steel balls were placed in the pan, and a new 80 mesh screen was positioned above the pan. The Ro-Tap shaker was run for another ten minutes without the hammer. The assembly was removed from the Ro-Tap shaker, and the steel balls were removed from the pan. The neotame from the pan was then transferred to the 80 mesh

screen, and the screen and pan were reassembled. The neotame and screen were then placed in the Ro-Tap shaker for ten minutes with the hammer. The fraction of neotame retained on the 80 mesh screen was weighed.

- 5 Hardness was calculated according to the formula: %  
hardness = (weight retained on 80 mesh/total weight of sample) X 100.

Table 2. Flake Characteristics.

10	sample	1	2	3	4
	flake thickness (mm)	2.27	1.85	1.77	2.19
15	density - loose (g/cc)	0.56	0.57	0.58	
	density - packed (g/cc)	0.65	0.65	0.67	
20	moisture (%)	4.43	4.47	4.55	4.24
	melting point (°C)	77.2/83.5	77.5/83.6	76.8/83.5	77.6/83.5
25	hardness (%)	92.80	91.00	93.40	92.20

Then the flakes were fed into a cone mill (model 197-S, Quadro Engineering Inc., Ontario, Canada) with 10 mesh  
30 conical sieve with a half inch hole in the bottom center at speed 10 (maximum) for size reduction and classification. The results of the granule formation and classification are shown in Table 3.

Table 3. Percent Retained.

sample	1	2	3	4
14 mesh	9.2	3.2	0	8.8
20 mesh	24.5	22.3	28.1	22.4
40 mesh	20.6	26.3	27.6	26.3
60 mesh	11.5	12.5	11	12.9
100 mesh	9.6	10.6	7.9	9.8
200 mesh	18.2	21.1	17.3	13.2
pan	4.4	3.9	4.1	4.6

EXAMPLE 2

A lab scale TF-Mini roller compactor (Vector Corp., Marion, IA) was used in conjunction with a cone mill and a Ro-Tap testing sieve shaker (model B, CE Tyler Combustion Engineering, Inc., Mentor, OH) for testing and producing granulated neotame. The neotame powder flowed well into the feed hopper. The compacted flakes were strong and had a "fused" appearance. The compactor did not make any significant crackling noises, indicating very efficient compaction without much air entrapment. The energy consumption of the rolls and feed screw were within the desired limits. The flakes were broken down into granular particles using a cone mill. The granulation was sieved to obtain a particle size that passed through 20 mesh and was retained on 60 mesh. This granulation was non-dusty, had a bulk density of 0.6 g/cc (initial powder was 0.4 g/cc) and very good flow properties. HPLC analysis showed that there was no degradation of neotame during this granulation process.

# Physical Properties of Roller Compacted Neotame Granules

Roller compacted neotame obtained from Examples 1 and 2  
5 was divided into various particle size ranges using an  
Alpine Air Jet Sifter (model A200LS, Hosokawa Micron  
Powder Systems, Summit, NJ). The particle size ranges  
were: 20-60 mesh, 60-100 mesh, 100-200 mesh and through  
200 mesh. These samples were tested for bulk density,  
10 flowability and dissolution rate. The results are  
shown in Table 4.

In particular, bulk density (loose) was measured using  
a cup of known volume. The cup was filled with sample,  
15 excess was removed and the sample was weighed.

The flowability of each sample was measured using a  
stainless steel funnel (orifice diameter 0.270"). The  
time taken for the sample to flow out through the  
20 orifice of the funnel was measured using a stop watch.

The dissolution rate of each sample was measured as a  
function of absorbance at 258 nm using a  
spectrophotometer. Sample (0.015 g) was added to 150 g  
25 deionized water at 20°C. The water was continuously  
stirred, and absorbance was measured versus time until  
it reached its highest value and became constant. The  
time required to reach the highest level of absorbance  
has been reported as "dissolution rate".

Table 4. Characteristics of Roller Compacted Neotame

sample	bulk density (loose) (g/cc)	flowability (g/sec)	dissolution rate (min)
20-60 mesh	0.59	3.30	16
60-100 mesh	0.55	4.50	3
100-200 mesh	0.51	4.65	1.5
through 200 mesh	0.39	no flow	1

The above data shows that the physical properties (bulk density, flowability, dissolution) of neotame granules can be modified by using different particle size ranges. This can help in creating value-added neotame granular forms tailored for specific applications, based on the requirements of the application.

Other variations and modifications of this invention will be obvious to those skilled in this art. This invention is not to be limited except as set forth in the following claims.